II. REMARKS

Preliminary Remarks

Claims 1, 10, 15, 19, 49 and 50 are amended, claims 2, 4-9, 17, 18, 20-25, 42, 43, 45-48 and 51-56 are canceled, and new claims 57 and 58 are added by this response. Claims 1, 10-15, 19, 49, 50, 57 and 58 are pending following entry of the amendment.

Claim 1 is amended to be directed to a method for the treatment or prevention of C-reactive protein (CRP)-mediated tissue damage in a subject suffering from myocardial infarction or stroke, comprising administering to the subject an effective amount of a compound capable of inhibiting the binding of CRP to a ligand thereof, wherein the compound comprises phosphocholine or a derivative thereof and binds to the calcium-dependent ligand binding site of CRP so as to interfere with binding of CRP to the ligand; and wherein the tissue damage results from myocardial infarction or stroke occurring as a complication of atherosclerosis in the subject. Support for the amendment is found in the specification, *e.g.*, on page 7, lines 2-4 and lines 14-18.

Claims 10 and 15 are amended to depend on claim 1, and claim 19 is amended to depend on any one of claims 1, 10 or 15.

Claims 49 and 50 depend respectively on claims 1 and 10, and are amended to specify that the tissue damage that is treated or prevented by the claimed method results from stroke, in accord with the amendment of claim 1.

New claims 57 and 58 depend respectively on claims 1 and 10, and specify that the tissue damage results from myocardial infarction, also in accord with the amendment of claim 1.

The applicant does not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserves the right to pursue such subject matter in continuing applications.

Patentability Remarks

35 U.S.C. §112, first paragraph

Claims 1-2, 10-15, 17-25 and 42-56 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly enables one of skill in the art to treat atherosclerosis but does not provide enablement for preventing atherosclerosis or for treating or preventing tissue damage in general.

The applicant respectfully disagrees with the examiner's rejection; however, in order to expedite examination of this application, claim 1 is amended to specify that the tissue damage that is treated or prevented by the claimed method is tissue damage that results from myocardial infarction or stroke (cerebral infarction) occurring as a complication of atherosclerosis in the subject, and claims 2, 17, 18, 20-25, 42, 43, 45-48 and 51-56 are canceled. Accordingly, only claims 1, 10-15, 19, 49 and 50 of the rejected claims are pending. The applicant submits that the specification enables one of skill in the art to successfully practice the claimed method for treating or preventing CRP-mediated tissue damage in a subject resulting from myocardial infarction or stroke occurring as a complication of atherosclerosis without having to perform undue experimentation, as discussed below.

Background

Atherosclerosis is a slow lifelong disease, caused by accumulation of blood cholesterol in plaques under the inner surface of the arterial wall. If atherosclerosis becomes sufficiently severe it can reduce arterial blood supply to the heart, brain or periphery causing vascular insufficiency. More acutely, an atherosclerotic plaque can rupture, triggering thrombotic occlusion of the affected artery, a process known as an atherothrombotic event. The resulting loss of blood supply causes death of the cells in the tissue served by that artery, due to lack of oxygen. In these circumstances the cells die by a process known as necrosis, and necrosis caused by lack of arterial blood supply is referred to as ischemic necrosis. Death of tissue is referred to as infarction and may be caused in different ways, of which ischemic necrosis is the most common and important. Atherothrombotic events affecting the coronary arteries cause myocardial infarction (heart attack) while such events in the cerebral arteries cause cerebral infarction (stroke). These tissue damaging conditions, which are complications of

atherosclerosis, are the cause of death in about half of all individuals, and the leading cause of mortality in the industrialized world.

Enablement

The amended claims of the present application are directed to a method for the treatment or prevention of CRP-mediated tissue damage resulting from myocardial infarction or stroke in a subject that occurs as a complication of atherosclerosis in the subject. The present application describes results obtained using an experimental *in vivo* model system in which tissue damage is caused by obstruction of blood supply and provides the first, and up to the present time the only, direct *in vivo* demonstration that CRP exacerbates tissue damage. The present application provides the first experimental evidence that CRP contributes to tissue damage *in vivo*, and that removal of CRP function from a subject who has a tissue damaging condition involving elevated levels of CRP will treat or prevent tissue damage in that subject. As discussed in the applicant's reply to the previous official action, the beneficial effects of the claimed invention are obtained for any tissue damaging condition involving elevated levels of CRP. The disclosed invention is therefore generally effective in treating or preventing tissue damage associated with any condition involving elevated levels of CRP. In the example described in the application, rats were subjected to surgical coronary artery ligation, producing complete occlusion of arterial blood supply to a section of the left ventricle of the heart, resulting in myocardial infarction, and infarct size was compared between rats which received injections of human CRP and control rats receiving only vehicle. Infarct size gives a direct measurement of the amount of tissue damage in the subject. The results are indicated in the section bridging pages 29 and 30 of the present application, and in Table 2. Table 2 provides data that shows that in animals receiving human CRP the mean infarct size is increased to be about 40% larger than in control animals that do not receive CRP. These results therefore demonstrate that the extent of tissue damage *in vivo*, in this case resulting from infarction caused by ischemia, is directly affected by and increased in the presence of human CRP; *i.e.*, that human CRP directly exacerbates tissue damage *in vivo*.

Using a different experimental *in vivo* model system from that described in the present application, the inventor, Professor Mark Pepys, has demonstrated that human CRP contributes

to tissue damage in the brain in the manner previously demonstrated for the heart. Gill et al. (J. Cerebral Blood Flow & Metabolism, 24(11):1214-1218, 2004), which is co-authored by Prof. Pepys, describes experimental results that show that damage to brain tissue (infarct size) resulting from obstruction of blood supply is significantly greater in rats receiving human CRP than in control rats that do not receive CRP. *See* page 3, second paragraph of Gill et al., a copy of which was submitted with the response filed on November 29, 2004. The demonstration in Gill et al. that CRP contributes to tissue damage resulting from cerebral infarction therefore provides further compelling *in vivo* evidence that CRP contributes to tissue damage in general.

The present application provides evidence concerning conditions such as myocardial infraction and stroke that are associated with tissue damage that involves elevated levels of CRP, thereby permitting one of skill in the art to identify types of tissue damage that can be prevented or treated by the present invention. As described in the present application "CRP is the classical acute phase protein, the circulating concentration of which increases dramatically in response to most forms of inflammation, tissue injury and infection, and the value (*i.e.*, the amount of CRP) attained in most conditions correlates closely with the extent and activity of disease." *See* page 1, lines 11-15, citing an article by the present inventor in the Oxford Textbook of Medicine (3rd Ed., Vol. 2, 1996; identified as reference FR in the IDS filed July 9, 2001). This article teaches that a number of inflammatory and/or tissue damaging and conditions are associated with increased CRP production and major elevation of serum CRP concentration, including infections, allergic complications of infections, inflammatory disease, allograft rejection, malignant neoplasia, necrosis and trauma (*see* page 1528 and Table 2 on page 1529). The present application similarly teaches that inflammatory and/or tissue damaging conditions associated with elevated CRP levels for which tissue damage may be prevented or treated according to the claimed invention include infections, allergic complications of infection, inflammatory diseases, ischemic or other necrosis, traumatic tissue damage and malignant neoplasia (*see* page 6, lines 18-22). The application further identifies myocardial infraction and stroke as tissue-damaging complications of atherosclerosis for which tissue damage can be treated or prevented by the claimed invention (*see* page 7, lines 2-4 and 14-17). The application identifies tissue-damaging conditions associated with elevated CRP levels and describes therapeutic agents that can be administered to inhibit CRP and prevent or treat exacerbation of

tissue damage by CRP. Once in possession of the compelling and direct *in vivo* evidence provided in the present application, a person of skill in this art would have information sufficient to practice the invention as claimed. The application thus describes and provides guidance, direction, and working examples for treating and/or preventing the tissue damage that results from myocardial infarction or stroke (cerebral infarction) occurring as a complication of atherosclerosis in a subject.

***In vivo* data support**

The ability of one of skill in the art to successfully practice the claimed invention as described by the present application is further demonstrated by the additional experimental data obtained by the applicant that is described in the declaration pursuant to 37 C.F.R. § 1.132 by Prof. Mark Pepys that was submitted with the supplemental response filed on April 19, 2006. The data demonstrate again the specific exacerbation of tissue damage mediated by human CRP in the rat acute myocardial infarction model, and clearly show that *in vivo* administration of a specific inhibitor of CRP completely abrogates this pathogenic effect. *See* the data in Table I and the description of the results on pages 5-6 of the declaration. The inhibitor of CRP that was used to obtain the additional experimental results is the phosphocholine derivative 1,6-bis(phosphocholine)-hexane, which consists of a pair of phosphocholine molecules that are connected by a short (6-carbon) alkane linker. **The experimental results described in the declaration further demonstrate that the extent of tissue damage that occurs *in vivo* is directly related to and exacerbated by the presence of CRP in a subject.**

Specific points raised by Examiner

In discussing the grounds for the rejection under 35 U.S.C. §112, first paragraph, in the official action, the examiner contends that the specification "does not reasonably provide enablement for preventing atherosclerosis and for treating and/or preventing tissue damage in general." The examiner acknowledges that the applicant has provided evidence showing that an excess amount of CRP causes tissue damage, but argues that the claims encompass treating and/or preventing "all disorders," including atherosclerosis, cancers, Alzheimer's disease and viral infections, for which effective treatments are wanting and preventive methods are unknown. The examiner further argues that the underlying etiologies of atherosclerosis and

other diseases associated with tissue damage such as cancer and Alzheimer's disease are complex and unclear, that factors other than CRP may contribute to the tissue damage associated with these diseases, and that the pharmaceutical art is unpredictable, so that "each embodiment must be assessed of physiological activity" requiring undue experimentation. *See* pages 3-4 of the official action.

The applicant respectfully submits that the application is concerned with the treatment or prevention of tissue damage caused by high circulating concentration of CRP in subjects having certain underlying primary conditions. Experimental evidence in the present application and published by the applicant confirms that CRP contributes to tissue damage in general, and the present application further demonstrates that subjects having a certain range of conditions would be encompassed by the present application because those conditions involve elevated CRP levels. The application makes it explicitly clear that any individual with pre-existing tissue damage and simultaneously having increased CRP concentration is at risk of suffering exacerbation of the tissue damage and thus is a suitable candidate for beneficial treatment with a drug that inhibits CRP.

The applicant strongly disagrees with the examiner's allegation that the term "tissue damaging condition" as used in the application includes all disorders. As discussed above, the application clearly identifies a selected set of conditions associated with tissue damage accompanied by an elevated level of CRP, for which the disclosed method will operate successfully to treat or prevent CRP-mediated tissue damage. In particular, the application teaches that the tissue damage that is treated or prevented by the disclosed method is associated with a condition selected from the group consisting of an infection, an allergic complication of infection, an inflammatory disease, ischemic or other necrosis, traumatic tissue damage and malignant neoplasia. Furthermore, the examiner's specific mention of Alzherimer's disease, cancer, viral infections and atherosclerosis inappropriately ignores the fact that the present claims are related precisely to subjects who have high circulating concentrations of CRP. CRP values are not significantly or substantially increased in patients with Alzheimer's disease, or in most viral infections or in cancer unless the malignancy is extensive and/or metastatic. Also CRP values do not correlate with extent or severity of atherosclerosis and are not substantially

increased in individuals with atherosclerosis, unless they suffer an atherothrombotic event. The specification provides a sound and compelling scientific basis for the disclosed method for treating and/or preventing tissue damage associated with the identified tissue-damaging conditions in subjects who also have high concentrations of CRP. Nonetheless, in order to expedite prosecution, independent claim 1 is amended to be directed to a method for the treatment or prevention of CRP-mediated tissue damage resulting from myocardial infarction or stroke occurring as a complication of atherosclerosis in a subject. As discussed above, the applicant has described experimental results showing that CRP exacerbates tissue damage resulting from myocardial infarction and stroke, and all of the information needed by a person of skill in the art to successfully perform the method of the invention as claimed may be found in the application. The application therefore enables one of skill in the art at the time of filing to practice the claimed invention successfully without having to perform undue experimentation.

In view of the foregoing, withdrawal of the rejection of pending claims 1, 10-15, 19, 49 and 50 under 35 U.S.C. §112, first paragraph, is respectfully requested.

35 U.S.C. §103(a)

Claims 1, 2, 10-15, 17-25 and 42-56 are rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of Bhakdi et al. and Kitao, further in view of Yedgar et al. (U.S. Patent No. 5,064,817) and Wissner et al. (U.S. Patent No. 4,640,913).

The examiner describes Bhakdi et al. and Kitao as teaching that "the binding of CRP to LDL is known to be a factor of atherosclerosis" and that phosphorylcholine inhibits the binding of CRP to LDL (*see* paragraph 3 on page 4 of the official action). Yedgar is described as teaching that "various phosphorylcholine derivatives are known to be useful for treating pathological conditions including atherosclerosis," and Wissner et al. is described as teaching that "various phosphorylcholine derivatives are useful for treating hypertension." In view of these teachings, the examiner alleges that "it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to employ a phosphorylcholine compound, such as hexadecyl phosphorylcholine, for treating atherosclerosis." With respect to stroke, the examiner alleges that "a method known to be useful for treating the underline [sic]

etiology of a disorder would have been reasonably expected to be useful for treating or preventing the disorder. (*see* paragraph 5 on page 5 of the official action).

The applicant respectfully disagrees with the examiner's rejection. However, in order to expedite examination of this application, claim 1 is amended to be directed to a method for treating or preventing CRP-mediated tissue damage in a subject suffering from myocardial infarction or stroke, comprising administering to the subject an effective amount of a compound capable of inhibiting the binding of CRP to a ligand thereof, wherein the tissue damage results from myocardial infarction or stroke occurring as a complication of atherosclerosis in the subject, and claims 2, 17, 18, 20-25, 42, 43, 45-48 and 51-56 are canceled. Accordingly, only claims 1, 10-15, 19, 49 and 50 of the rejected claims are pending.

To establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *See* In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), *also* In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) citing In re Raynes, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992), *and* M.P.E.P. § 2142.

The applicant submits that the cited references fail to teach or suggest all of the limitations of the claimed invention. Neither the primary reference, Bhakdi et al., nor any of the secondary references, Kitao, Yedgar et al., and Wissner et al., considered separately or in combination, teaches or suggests a method for treating or preventing CRP-mediated tissue damage resulting from myocardial infarction or stroke occurring as a complication of atherosclerosis in a subject, comprising administering a compound that binds to CRP and inhibits the binding of CRP to a ligand thereof, as specified in the present claims.

The applicant further submits that the combination of Bhakdi et al., Kitao, Yedgar et al., and Wissner et al. would not have provided one of ordinary skill in the art with a suggestion or motivation to practice the claimed method for treating or preventing CRP-mediated tissue damage in a subject suffering from myocardial infarction or stroke, comprising administering to the subject an effective amount of a compound that comprises phosphocholine or a derivative thereof and binds to the calcium-dependent ligand binding site of CRP and of inhibits the binding of CRP to a ligand thereof, wherein the tissue damage that is treated or prevented results from myocardial infarction or stroke occurring as a complication of atherosclerosis in the subject. Moreover, the combination of Bhakdi et al., Kitao, Yedgar et al., and Wissner et al. would not have provided one of ordinary skill in the art with a reasonable expectation that the claimed method could be performed successfully.

Bhakdi et al.

In the first place, and as discussed in the applicant's reply to the previous official action, the examiner's allegation that the Bhakdi et al. would have provided a suggestion or motivation to one of ordinary skill in the art at the time the invention was made to treat atherosclerosis by administering an agent that inhibits the binding of CRP to its ligand is incorrect. Phosphocholine has been known to be the highest affinity small molecule ligand for CRP since 1971, and it is known to be inhibitory for all known calcium dependent ligand binding interactions of CRP. The binding of CRP to LDL, first discovered and characterized by the applicant, Professor Pepys in 1984 and cited in the present application (ref. no. 5), led Prof. Pepys to make the first suggestion that CRP might be involved in atherosclerosis. Many subsequent publications have included similar speculations but **up to the present time there have been no observations that demonstrate any actual role of CRP in atherosclerosis, atherogenesis or atherothrombosis *in vivo*. Indeed, as stated above, the overwhelming weight of current published evidence, both from clinical studies and animal models, indicates that CRP has neither an atherogenic nor an atheroprotective role *in vivo*.**

Bhakdi et al. demonstrates *in vitro* binding of CRP to E-LDL, and shows *ex vivo* that CRP is co-localized with E-LDL in coronary artery specimens. Based on the demonstration that CRP enhances the *in vitro* conversion of complement factor C3 by E-LDL, Bhakdi et al.

speculates that CRP may promote pathological events in atherogenesis via complement activation. However, Bhakdi et al. presented no evidence that CRP promotes or causes atherogenesis in any way, or has any pathological effect on tissue lesions. In fact, as noted above, while there has been considerable speculation over the years, **there is no *in vivo* evidence at all that CRP causes atherosclerosis or atherothrombosis**.

The present claims are amended to be directed to a method for treating or preventing CRP-mediated tissue damage resulting from myocardial infarction or stroke occurring as a complication of atherosclerosis in a subject that comprises administering to the subject suffering from myocardial infarction or stroke an effective amount of a compound that comprises phosphocholine or a derivative thereof and binds to CRP and of inhibits the binding of CRP to a ligand thereof. **Bhakdi et al. provides no suggestion or motivation to one of ordinary skill in the art to treat or prevent CRP-mediated tissue damage resulting from myocardial infarction or stroke occurring as a complication of atherosclerosis by administering a compound that inhibits the binding of CRP to its ligand to the subject suffering from the myocardial infarction or stroke. Nor does Bhakdi et al. provide one of ordinary skill in the art with a reasonable expectation that such a method would operate successfully to treat or prevent CRP-mediated tissue damage resulting from the myocardial infarction or stroke.**

The combination of Bhakdi et al. with Kitao, Yedgar et al., and Wissner et al. would not have remedied the deficiencies of Bhakdi et al. and provided one of ordinary skill in the art with suggestion or motivation to practice the method as claimed, nor would the combined references have provided one of ordinary skill in the art with a reasonable expectation that the claimed method would operate successfully to treat or prevent CRP-mediated tissue damage resulting from myocardial infarction or stroke in the subject.

Kitao

The Kitao abstract teaches that the *in vitro* binding of CRP to serum lipoproteins is inhibited by phosphorylcholine and 6-amino-n-caproic acid, and indicates that “the relationship of CRP and atherosclerosis is discussed." Kitao does not describe or suggest a role of CRP in the pathogenesis of atherosclerosis or atherothrombosis.

Yedgar et al. and Wissner et al.

Yedgar et al. describes a method that for treating pathological conditions associated with oversecretion of PLA_2, including atherosclerosis, including phosphocholine derivatives such as phosphatidylethanolamine and phosphatidylserine derivatives. Wissner et al. describes phosphocholine derivatives that are suggested to have anti-hypertensive action.

Neither Kitao, Yedgar et al., nor Wissner et al. describes or suggests that CRP-mediated tissue damage resulting from myocardial infarction or stroke occurring as a complication of atherosclerosis in a patient can be treated or prevented by administering to the patient with myocardial infarction or stroke a compound that inhibits the binding of CRP to its ligand, in accord with the invention as claimed. Accordingly, one of ordinary skill in the art at the time the invention was made would not have been motivated to combine the teachings of Kitao, Yedgar et al. and Wissner et al. with those of Bhakdi et al., to obtain the claimed invention. Moreover, as discussed above, prior to the applicant's discovery that CRP exacerbates tissue damage resulting from a tissue-damaging condition such as infarction, as described in the present application, it was not known and could not have been predicted that tissue damage resulting from myocardial infarction or stroke in a patient can be treated or prevented by administering a compound that inhibits the binding of CRP to its ligand. The combined teachings of Bhakdi et al., Kitao, Yedgar et al. and Wissner et al. therefore would not (and could not) have provided one of ordinary skill in the art at the time the invention was made with a reasonable expectation that the claimed method would operate successfully to treat or prevent CRP-mediated tissue damage resulting from myocardial infarction or stroke.

For the foregoing reasons, the applicant submits that the examiner has not established a *prima facie* case of obviousness, and respectfully requests that the rejection of pending claims 1, 10-15, 19, 49 and 50 under 35 U.S.C. §103(a) in view of Bhakdi et al. in combination with Kitao et al., Yedgar et al., and Wissner et al., be withdrawn.

III. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

/ thomas a cawley jr /

Date: December 29, 2006 By_____

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